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Final Report on the Safety Assessment of Polyoxymethylene Urea[1]

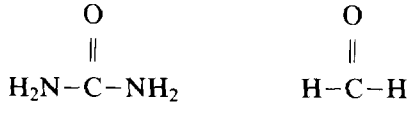
Abstract: Polyoxymethylene Urea is a variable molecular weight polymer formed in stages from the condensation reaction of urea with formaldehyde. It is used in a wide range of cosmetic formulations as a bulking agent and to form the outer shell of microcapsules. Because of the nature of the polymerization process, residual formaldehyde is present at levels typically between 17 and 30 ppm. Polyoxymethylene Urea shows low toxicity. The oral LD_{50} in rats was 10 g/kg for the bulk material and 20 g/kg when the microcapsule form was used. Polyoxymethylene Urea was a mild skin irritant and caused mild, transient ocular irritation in rabbits. Ames tests were negative for mutagenesis. Clinical data showed no irritation or sensitization. On the basis of the data, it is concluded that Polyoxymethylene Urea is safe for use as a cosmetic ingredient. A previous determination, however, that the concentration of free formaldehyde in cosmetic formulations should not exceed 0.2% was considered appropriate for this ingredient as well. Likewise, the previous finding that the safety of formaldehyde was not ensured in cosmetic products intended to be aerosolized is extended to this ingredient. **Key Words:** Polyoxymethylene Urea—Cosmetics.

Polyoxymethylene Urea is a synthetic polymer used by the cosmetic industry as a bulking agent and to form the outer shell of microcapsules. The Cosmetic Ingredient Review (CIR) Expert Panel reviewed formaldehyde in 1984, and the Final Report on the Safety Assessment of this ingredient can be found in the *Journal of the American College of Toxicology*, Vol. 3, No. 3 (Elder, 1984).

CHEMISTRY

Definition and Structure

Polyoxymethylene Urea (CAS No. 9011-05-6) is a reaction product of urea with formaldehyde (Nikitakis et al., 1991). The chemical structure of Polyoxymethylene Urea is dependent upon its degree of polymerization (Franklin Institute Research Laboratories, 1978). The components of the resin are given here (Nikitakis et al., 1991; Elder, 1984):



Urea Formaldehyde

[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Other names for Polyoxymethylene Urea are Urea/Formaldehyde Resin and Urea, Polymer with Formaldehyde (Nikitakis et al., 1991).

Properties

Low molecular weight Polyoxymethylene Ureas are viscous liquids (neutral or alkaline pH) or powdery solids (acid pH) that are readily degraded in the environment, releasing free formaldehyde (Franklin Institute Research Laboratories, 1978). Liquid Polyoxymethylene Urea has a clear to milky appearance, a formaldehyde or amine odor (Georgia-Pacific Corp., 1983*a–c*), a pH range of 6–9, and a viscosity range of 10–2,000 centipoises (Formaldehyde Institute, 1984). Samples of liquid Polyoxymethylene Urea had a boiling point of 212°F (Georgia-Pacific Corp., 1983*a–c*) and a specific gravity of ~1.4 (BASF Wyandotte Corp., 1984). Liquid Polyoxymethylene Urea is soluble in water and alcohol (Franklin Institute Research Laboratories, 1978).

Low molecular weight products are converted to highly polymerized Polyoxymethylene Ureas by heat (heat cured) or acid (acid cured). They are inert solids that are colorless, odorless, and stable under ambient conditions. These solids are insoluble in cold water, but decompose in boiling water and hot, strong acids and alkalis (Franklin Institute Research Laboratories, 1978).

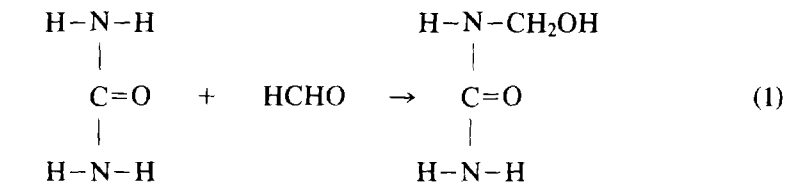
Method of Manufacture

Polyoxymethylene Urea is manufactured to yield specific working properties, so no precise chemical or physical analyses of the reaction products are available. The general ranges for the chemical composition of Polyoxymethylene Urea prior to curing are as follows (Formaldehyde Institute, 1984):

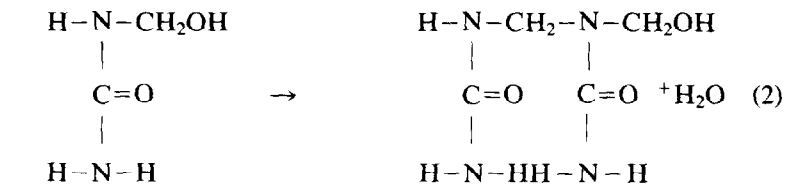
Mole ratio; urea to formaldehyde	1:1.1–1:2.5
% solids	6–9
% free formaldehyde	0.2–5
% free urea (per HPLC)	0–5
% monomethylolurea (per HPLC)	0–14
% dimethylolurea (per HPLC)	0–8

Polyoxymethylene Urea is formed in stages from the condensation reaction between urea and formaldehyde. Typically, a mixture of mono- and dimethyl-urea is initially formed, and combined formaldehyde is present in the complex polymer in subsequent stages. Formaldehyde is present as a dimethylene ether bridge ($-CH_2OCH_2-$), a methylene bridge ($-CH_2-$), and as methylol end groups ($-CH_2OH$). Free formaldehyde is also present in variable amounts. The three combined forms of formaldehyde are hydrolyzed when treated with base, yielding free formaldehyde (Breysse, 1985).

A typical reaction is depicted in the following three steps (National Research Council, 1981):



(1)



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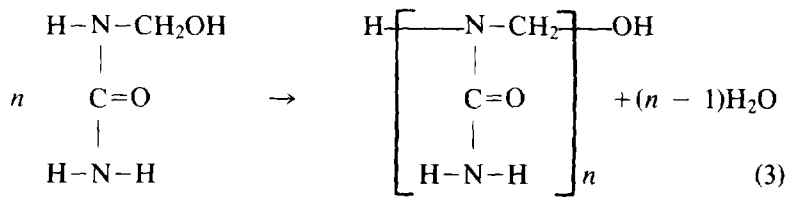

(3)

Impurities

During the production of commercial Polyoxymethylene Urea, additional formaldehyde is used to react with unreacted $-NH_2$ groups and to provide chemical cross-links between polymer chains. An excess of formaldehyde causes faster polymerization and increases cross-linking, but is not used up in the reaction. As a result, unreacted formaldehyde may be present in the final product, which may slowly diffuse from it. Formaldehyde may also be formed and released from the resin by hydrolysis when the resin is exposed to water or to a humid atmosphere (National Research Council, 1981).

Fourteen typical Polyoxymethylene Ureas were analyzed for monomeric species using high performance liquid chromatography (HPLC). Urea and monomethylolurea were found at concentrations ranging from 0.00 to 11.69% and 0.20 to 13.93% (% liquid resin basis), respectively. The weight percentage of free formaldehyde ranged from 0.16 to 2.58% (Decatur Analytical Chemistry Group, 1984).

Polyoxymethylene Urea has been reported to contain up to 10% methylolurea (Borden, 1983).

Ludlam (1973) monitored the concentrations of urea, monomethylolurea, and dimethylolurea in two samples of Polyoxymethylene Urea over 60 days using thin-layer chromatography. Sample 1 had additional urea (11.5%) added at the end of its manufacturing process to reduce the concentration of free formaldehyde. Additional urea was not added to Sample 2. The urea in Sample 1 decreased from 9% on day 1 to ~2% after 60 days. From day 1 to day 17, monomethylolurea and dimethylolurea increased from 4% each to 9 and 8%, respectively, and then de-

creased to 5 and 6% on day 60. In Sample 2, the concentration of urea was <0.5% over the 60-day period. Monomethylolurea decreased from 1.5% on day 1 to <0.5% on day 60. The concentration of dimethylolurea decreased from 10 to ~6% on day 10, increased to 8% around day 30, and then tapered off to ~7% on day 60. Methylenediurea and dimethylolmethylenediurea were also isolated by the chromatograms at up to 1 and 5%, respectively.

USE

Cosmetic Use

Polyoxymethylene Urea is a synthetic polymer used in cosmetic formulations as a bulking agent (Nikitakis, 1988). It is also used to form the outer shell of microcapsules. In such a form, Polyoxymethylene Urea is used in its solid state with a neutral pH. One supplier reported that although the maximum allowable free formaldehyde level is set at 200 ppm, the amount of free formaldehyde found in most lots of Polyoxymethylene Urea is within the range of 17–30 ppm (3M, 1993).

The product formulation data submitted to the Food and Drug Administration (FDA) in 1993 reported that Polyoxymethylene Urea was used in a total of 28 cosmetic product formulations (Table 1). Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, product formulation data submitted to the FDA in 1984 indicated that Polyoxymethylene Urea was used at concentrations up to 5% in eye shadows, blushers, and face powders and up to 1% in rouges. Polyoxymethylene Urea was not reported as being used in perfumes, lipsticks, basecoats and undercoats, or other manicuring preparations in 1984 (FDA, 1984).

In 1992 it was reported to the Cosmetic, Toiletry, and Fragrance Association (CTFA) that Polyoxymethylene Urea was used at up to 2% in cosmetic formulations (CTFA, 1992).

The skin is directly exposed to products containing Polyoxymethylene Urea, and the potential exists for it to come into contact with the eyes. Products containing this ingredient may be used daily for extended periods of time.

TABLE 1. *Cosmetic product formulation data for Polyoxymethylene Urea (FDA, 1993)*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Eye shadow	569	6
Perfumes	248	1
Blusher (all types)	255	4
Face powders	266	8
Lipstick	850	2
Rouges	31	4
Basecoats and undercoats	44	2
Other manicuring preparations	70	1
Total	—	28

Noncosmetic Use

Polyoxymethylene Urea is approved for use in resinous and polymeric coatings coming into contact with foods and may be used in polysulfide polymer–polyepoxy resins for contact with dry foods (Rothschild, 1988). Polyoxymethylene Urea is also used as a bonding agent in the manufacture of particleboard, chip board, and interior plywood, in coatings for paper products and fiberglass insulation, and in the formulation of foam insulation (Breysse, 1985).

Polyoxymethylene Urea is also used in the manufacture of textiles, most commonly wrinkle-resistant clothing fabrics (Marcussen, 1962; Hatch and Maibach, 1986).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Five male and five female rats were administered 10 g/kg of liquid Polyoxymethylene Urea by gavage. No deaths occurred during the 14-day observation period (Litton Bionetics, 1977*a*).

In similar studies with rats, LD_{50} values were reported as >5.8 g/kg (Ciba-Geigy Corp., 1973*a*), >5.2 ml/kg for liquid Polyoxymethylene Urea (Anonymous, 1986*a*), 5.2 g/kg for spray-dried urea–formaldehyde powdered glue (Wells Laboratories, 1973*a*), and 10,000 and 15,800 mg/kg for undiluted Polyoxymethylene Urea (Younger Laboratories, 1974, 1979).

The oral LD_{50} for microcapsule shell walls made of Polyoxymethylene Urea was >20 g/kg for rats (3M, 1991).

Dermal

The dermal LD_{50} for Polyoxymethylene Urea for Sprague–Dawley rats was >2.1 g/kg (Ciba-Geigy Corp., 1973*b*).

Four rabbits had 5,000 mg/kg Polyoxymethylene Urea applied under occlusive patches to the intact or abraded skin of their abdomens for 24 h. The animals were monitored for 2 weeks. All of the rabbits survived the study and no lesions were found at necropsy (Litton Bionetics, 1977*b*).

No deaths occurred when 10 rabbits had 2.2 g/kg of liquid Polyoxymethylene Urea applied to their skin for 24 h (Anonymous, 1986*b*).

In similar studies, 2.2 g/kg or urea–formaldehyde powdered glue and 7,940 mg/kg Polyoxymethylene Urea were not dermatotoxic to four and two rabbits, respectively (Wells Laboratories, 1973*b*; Younger Laboratories, 1974, 1979).

Inhalation

The LC_{50} for rats exposed to Polyoxymethylene Urea for 4 h with a 7-day observation period was >167 mg/m^3 air (Ciba-Geigy Corp., 1973*c*).

Ten Charles River CD rats were exposed to a test atmosphere of 2 mg/kg of Polyoxymethylene Urea for 1 hr. The animals were observed for 14 days and

necropsy was performed at the end of the study. All of the rats survived the study, no signs of toxicity were observed during the study, and no lesions were found at necropsy (Litton Bionetics, 1977*c*).

In similar studies, no signs of toxicity were observed in either Sprague–Dawley rats tested with 5.0 m/L Polyoxymethylene Urea (Younger Laboratories, 1979) or mice exposed to 200 mg/L liquid Polyoxymethylene Urea (Anonymous, 1986*c*) or 200 mg/kg urea–formaldehyde powdered glue (Wells Laboratories, 1973*c*).

Subchronic Inhalation Toxicity

A 28-day inhalation study of a formulation containing 66–71% Polyoxymethylene Urea and cellulose was conducted using a dust-aerosolized form of the material. Ten male Fischer 344 rats were exposed to gravimetric concentrations of 99.9 mg/m^3 of the formulation 6 h/day for 5 days during the first 3 weeks and then for 4 days/week during the last week of the study. The mean mass median aerodynamic diameter of the formulation was 2.8 μm. A control group of rats was exposed to ambient air only. The rats were monitored throughout the study for toxicity; hematologic analyses and urinalyses were conducted at the end of the study, and necropsy was performed on all of the animals.

All of the animals survived the study, and at no time was there clinical evidence of toxicity. A mild reduction in body weight gain was observed among the treated animals, but it was not statistically significant. Blood and urine analyses were normal. At necropsy, the absolute kidney and kidney/brain weight values were decreased, but no gross lesions were observed in these organs. The authors noted that no histologic evaluation was made of the kidneys. A slight increase in the lung/body weight value was found, which the authors noted was consistent with the deposition of dust and the influx of phagocytic and inflammatory cells into the lungs. Seventy percent of the rats had interstitial pneumonia and 30% of these rats also had minimal, multifocal interstitial fibrosis (Bushy Run Research Center, 1987).

Dermal Irritation

In the acute dermal toxicity study conducted by Litton Bionetics (1977*b*) (described earlier in this report), the four rabbits tested were monitored for signs of irritation after having Polyoxymethylene Urea applied under occlusive patches to the intact and abraded skin of their abdomen. All the animals had signs of slight erythema on the first and second days of treatment only.

Four patches containing 0.5 ml of liquid Polyoxymethylene Urea were placed for 24 h on the intact and abraded skin of six rabbits. The sites were scored when the patches were removed 48 h later. The primary irritation index was 0.833 (maximum possible score: 8). Polyoxymethylene Urea was a minimal irritant (Anonymous, 1986*d*).

In similar studies, six rabbits were tested with Polyoxymethylene Urea glue, undiluted Polyoxymethylene Urea, and powdered Polyoxymethylene Urea in

polyethylene glycol 400. The primary skin irritation index (maximum possible score: 8) was 2.0 for the glue (Wells Laboratories, 1971*a*), 0 for the resin (Younger Laboratories, 1974, 1979), and 0.1 for the powder (Ciba-Geigy Corp., 1973*d*).

Polyoxymethylene Urea in microcapsule form was applied under occlusive patches to the intact and abraded skin of six albino rabbits for 24 h. The application sites were scored at 24 and 72 h. Polyoxymethylene Urea was minimally irritating. Primary irritation scores in two separate studies were 0.0 and 0.14 of a maximum possible score of 8.0 (3M, 1991).

Ocular Irritation

An ocular irritation test was conducted using six rabbits. The right conjunctival sac of each rabbit was instilled with 0.1 ml of liquid Polyoxymethylene Urea. The left eye served as an untreated control. The eyes were scored at 24, 48, 72, and 96 h and on day 7. Minimal conjunctivitis was observed during the 24- and 48-h readings, but it disappeared by 72 h (Anonymous, 1986*e*).

In a similar study, six albino rabbits had 0.1 ml Polyoxymethylene Urea instilled into the conjunctival sac of one eye, and the eyes of three rabbits were rinsed after 30 s of exposure. A small ulcer was found on the cornea of one unrinsed eye at 24 h, and corneal irritation was present in four of the animals. All signs of irritation disappeared after 72 h (Ciba-Geigy Corp., 1973*e*).

In another study, a Polyoxymethylene Urea glue was tested for ocular irritation. A 0.1-g dose was instilled in one eye of each of six rabbits, and the eyes were observed for 7 days. No irritation was observed at any time (Wells Laboratories, 1971*b*).

Six New Zealand albino rabbits each had 0.1 ml of undiluted Polyoxymethylene Urea instilled in one eye, and the eyes were scored at 1, 24, 48, and 72 h. The eyes of all the rabbits had slight erythema and copious discharge at the 1-h reading; all signs of irritation disappeared by the 24-h reading (Younger Laboratories, 1979).

Similar results were reported in a study using three rabbits. Undiluted Polyoxymethylene Urea (0.1 ml) caused erythema and edema at the 1-h reading, which subsided by the 24-h reading and disappeared by the 72-h reading (Younger Laboratories, 1974).

With use of a conventional Draize procedure with albino white rabbits, Polyoxymethylene Urea in its microcapsule form was tested for ocular irritation. The maximum irritation score during the study (8.6 of a possible maximum of 110.0) was observed 1 h following instillation. All signs of irritation subsided by 72 h, and the eyes remained clear until the end of the study at day 7 (3M, 1991).

MUTAGENICITY

Polyoxymethylene Urea was tested for bacterial mutagenic activity in the Ames test, using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. Polyoxymethylene Urea was tested in triplicate at concentrations of 1, 10, 100, 500, and 1,000 μl/plate both with and without metabolic activation with S-9. *N*-Methyl-1-*N*-nitro-*N*-nitrosoguanidine, 9-aminoacridine, and 2-nitrofluorene

were used as the positive mutagenic controls for the inactivation assay, and 2-aminoanthracene was the positive control for the activation assay. Polyoxymethylene Urea was not mutagenic for all five strains both with and without metabolic activation (Hill Top Research, 1980).

A 50/50 polyester/cotton fabric treated with Polyoxymethylene Urea was tested for mutagenic activity both with and without metabolic activation (S-9) in the Ames test. The strains of *S. typhimurium* used were TA1535, TA1537, TA1538, TA98, and TA100. A 0.5-in^2 test fabric was placed on the surface of $\sim 10^8$ cells mixed with molten agar supplemented with biotin and histidine, and the overlay with cells was spread over the surface, including the fabric. The plates were incubated for 48 h at 37°C. The positive controls for the unactivated samples were methylnitrosoguanidine, 2-nitrofluorene, and quinacrine mustard; positive controls for the activated samples were 2-anthramine, 2-acetylaminofluorene, and 8-aminoquinoline. The test fabric was negative in both systems for all of the *S. typhimurium* strains tested (Litton Bionetics, 1977*d*).

Morin and Kubinski (1978) investigated the ability of Polyoxymethylene Urea to induce macromolecular complexes. Specifically, they investigated the effects of Polyoxymethylene Urea on the binding of *Escherichia coli* DNA to *E. coli* cells. *E. coli* [^{32}P]DNA and *E. coli* cells were incubated with Polyoxymethylene Urea alone or with Polyoxymethylene Urea in the presence of either lysozyme or mouse liver extract. Polyoxymethylene Urea was tested at concentrations ranging from 0.3 to 6%. After a 60-min exposure period, the cellular fraction was isolated and the percentage of [^{32}P]DNA retained with the cellular sediment was measured. The only significant increase in binding between the DNA and the bacterial cells occurred in the presence of both Polyoxymethylene Urea and liver extract: 2.49, 4.03, 6.74, and 26.80% of the [^{32}P]DNA was recovered from the solutions containing 0.3, 0.6, 3, and 6% Polyoxymethylene Urea. The recovery of [^{32}P]DNA from solutions treated with 0.3 and 3% Polyoxymethylene Urea alone was 0.05 and 0.58%, respectively. A solution treated with liver extract alone had 1.22% of the [^{32}P]DNA recovered, and an untreated control sample had 1.12% recovered.

Using density gradient centrifugation, the authors investigated the sedimentation rate of the various test solutions. There was no significant change in the sedimentation rate of DNA treated with Polyoxymethylene Urea alone or with mouse liver extract alone. However, when DNA was incubated with both Polyoxymethylene Urea and liver extract, sedimentation occurred more quickly than with the control DNA, indicating the formation of complexes between DNA molecules and/or between DNA and proteins present in the extract. The authors suggested in this early work that DNA damage by certain chemicals would lead to DNA-DNA and/or DNA-protein crosslinking that could be detected in sedimentation profiles. The implication from this study, therefore, is that metabolically activated Polyoxymethylene Urea produces DNA damage. This, in turn, suggested to the authors the possibility that this ingredient could be mutagenic or carcinogenic. While other data in this section appear to indicate little mutagenic potential, the carcinogenic potential of formaldehyde residues in Polyoxymethylene Urea is discussed next.

CARCINOGENICITY

No data on the carcinogenic potential or the developmental toxicity of Polyoxymethylene Urea were available. However, carcinogenicity data were available about its components. According to the International Agency for Research on Cancer (IARC), "there is sufficient evidence that formaldehyde gas is carcinogenic to rats." They noted that concentrations of formaldehyde that cause nasal tumors also cause acute degeneration, necrosis, inflammatory changes, and increased cell replication (hyperplasia) of the nasal mucosa of rats and mice following inhalation exposure (IARC, 1982). Fleischman et al. (1980) reported that there was no evidence of carcinogenic effects when C57B1/6 mice and Fischer 344 rats were fed 0.45, 0.9, and 4.5% urea in their diets for 12 months.

CLINICAL ASSESSMENT OF SAFETY

Toxicity from exposure to Polyoxymethylene Urea appears to be primarily related to the presence of formaldehyde gas in the environment (Harris et al., 1981). In 1984, CIR published a safety report on formaldehyde, reporting that formaldehyde is an ocular and respiratory irritant and may induce hypersensitivity. Under experimental conditions, formaldehyde is teratogenic, mutagenic, and can induce neoplasms. The CIR Expert Panel stated that it could not be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. However, in other cosmetic formulations, formaldehyde is safe to the great majority of consumers. The Panel believes that because of the skin sensitivity of some individuals to this agent, cosmetic products containing formaldehyde should be formulated to ensure use at the minimal effective concentration, not to exceed 0.2% measured as free formaldehyde (Elder, 1984).

Health Effects of Formaldehyde

Table 2 summarizes data on human exposure to formaldehyde at various airborne concentrations. The severity of specific health effects appears to be dose related (National Research Council, 1981). Among some of the reported effects

TABLE 2. *Reported human health effects of formaldehyde at various airborne concentrations (National Research Council, 1981)*

Health effects reported	Approx. formaldehyde concentration (ppm)
None	0–0.5
Neurophysiologic effects	0.05–1.50
Odor threshold	0.05–1.0
Eye irritation	0.01–2.0[a]
Upper airway irritation	0.10–25
Lower airway and pulmonary effects	5–30
Pulmonary edema, inflammation, pneumonia	50–100
Death	100+

[a] The low concentration (0.01 ppm) was observed in the presence of other pollutants that may have been acting synergistically.

were neurophysiologic changes (as demonstrated by alterations in optical chronaxy, electroencephalogram, etc.); eye, skin, nose, throat, and bronchial irritation; and pulmonary lesions (pneumonia, bronchial inflammation, pulmonary edema). Death may result from exposure to formaldehyde vapor at concentrations of ≥100 ppm (National Research Council, 1981; Fielder, 1981). The effects of formaldehyde arising from occupational exposure have been reviewed in some detail by Fielder (1981). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a limit of 2 ppm (~2.5 mg/m^3) for occupational exposure (ACGIH, 1980).

Formaldehyde is irritating to the eyes. Ocular irritation to atmospheric formaldehyde generally occurs at concentrations of 0.05–0.5 ppm; lacrimation occurs at concentrations of 4–20 ppm. Aqueous solutions of formaldehyde accidently splashed into the eye have caused such injuries as eyelid and conjunctival edema, corneal opacity, and loss of vision (National Research Council, 1981; Fielder, 1981). Numerous studies demonstrating the ocular irritation by formaldehyde have been reviewed by the National Research Council (1981).

Upper airway irritation to formaldehyde vapor frequently occurs at 1–11 ppm (irritation has been recorded at concentrations as low as 0.1 ppm). Formaldehyde can cause alterations in the nasal defense mechanisms, which may include a decrease in mucociliary clearance and loss of olfactory sensitivity. Lower airway irritation frequently is reported at 5–30 ppm. Chest radiographs of persons exposed to these concentrations are usually normal, except for occasional reports of accentuated bronchovascular marks; however, pulmonary function tests may be abnormal. Pulmonary edema and pneumonitis and death can result from very high airborne formaldehyde concentrations (50–100 ppm) (National Research Council, 1981).

Formaldehyde inhalation has caused bronchial asthma and asthma-like symptoms in humans. Although asthmatic attacks are in some cases specifically attributable to either formaldehyde sensitization or allergy, the gas seems to act more commonly as a direct airway irritant in persons who have bronchial asthmatic attacks from other causes. The exact mechanism for asthma induction by formaldehyde is not known (National Research Council, 1981).

Formaldehyde has caused contact urticaria and it is a known skin irritant and sensitizer. Allergic contact dermatitis in persons both occupationally and nonoccupationally exposed to formaldehyde is well recognized (Fielder, 1981). The North American Contact Dermatitis Group (NACDG) reported a 5% incidence of skin sensitization (124 reactions) among 2,374 patients exposed to 2% formaldehyde in aqueous solution (NACDG, 1980). Most sensitized persons can tolerate topical axillary products containing formaldehyde at up to 30 ppm (Jordan et al., 1979); with increasing concentrations, an increased frequency of responders is seen (Marzulli and Maibach, 1974). The National Research Council (1981) reported that aqueous formaldehyde solutions produce skin irritation under occlusive conditions in some sensitized individuals at concentrations as low as 0.01%. In unpublished data reported by the CTFA, cosmetic products containing 0.000185–0.0925% formaldehyde were practically nonirritating and nonsensitizing in a total of 1,527 subjects in 18 separate tests (Elder, 1984).

Dermal Irritation to Urea

The irritancy potential of urea in different vehicles was investigated by Agner (1992). Seventeen healthy volunteers were patch tested on their upper arm with 20% urea in either petrolatum or water using Finn chambers. Separate test chambers with the two vehicles were used as controls. The chambers were removed after 24 h, and the sites were scored at 24 and 48 h. Cutaneous blood flow, skin thickness, and transepidermal water loss were also assessed.

Urea caused visible irritant reactions with both vehicles, but irritant reactions were found significantly more frequently with 20% urea in petrolatum. A total of 12 reactions were observed with urea in petrolatum, 4 with urea in water, 1 in the petrolatum control, and 4 with the water control. Urea in petrolatum significantly increased blood flow and skin thickness and increased transepidermal water loss. These effects were transient, subsiding within 24 h. Urea in water did not increase blood flow over that of its preapplication value. A significant increase in skin thickness was observed with urea in water, but this was not significantly different from the water control values. No significant changes in barrier function were observed with urea in water.

The chamber–scarification test was used to assess the irritancy of 7.5 and 30.0% urea. Five subjects had criss-cross scratches made on their forearms, and chambers with 100 μl urea in water were applied to the scarified areas once a day for 3 consecutive days. Readings of the skin were taken daily. The authors reported that 7.5% urea was a slight irritant and that 30.0% urea was a "marked" irritant at 72 h (Frosch and Kligman, 1977).

In a double-blind cumulative irritancy study, 16 patients had 0.3 mg of a 10% urea base and a 20% urea cream with nonlipid emollients applied under occlusive patches to a paraspinal location daily for 21 days. The sites were evaluated for irritancy every 24 h. None of the subjects reacted to the 10% urea base, but all of the subjects had irritant reactions with the 20% urea cream. The cumulative irritancy scores ranged from 7.5 to 43.5 (maximum possible score: 81) (Fair and Krum, 1979).

Dermal Irritation and Sensitization to Polyoxymethylene Urea

A human patch test using Polyoxymethylene Urea in its microcapsule form was conducted using 207 subjects. Following a modified Draize technique, microcapsules were applied to the skin every other day for a total of 10 applications. A challenge application was made after a 2-week nontreatment period. No sensitization reactions were observed (3M, 1991).

Polyoxymethylene Urea was tested for sensitization in a human repeated insult patch test. A series of nine induction patches containing undiluted Polyoxymethylene Urea (amount not specified) were applied to the skin of 50 subjects for 24 h. The patches were applied on Monday, Wednesday, and Thursday and the sites were graded at the time of patch removal. After a 15-day nontreatment period, a challenge patch was applied for 24 h to a previously untreated site and the site was evaluated 24, 48, and 72 h after application. No signs of irritation or sensitization were observed (Industrial Bio-Test Laboratories, 1975).

Case reports of contact dermatitis from textiles treated with formaldehyde resins have been reported in the literature. Most cases of sensitization have been attributed to free formaldehyde (Marcussen, 1962; O'Quinn and Kennedy, 1965; Shellow and Altman, 1966; Schwartz, 1941), but a few studies have reported sensitivity to formaldehyde resins themselves (Malten, 1964; Hatch and Maibach, 1986). Most recently, Fowler et al. (1992) reported on 17 patients with contact dermatitis due to formaldehyde textile resins, who were patch tested with both the resins and formaldehyde alone. Five of the patients (30%) had positive responses to the resin alone, while the others responded positively to both the resins and formaldehyde.

Environmental and Occupational Exposure

Contact Dermatitis

Markuson et al. (1943) reported on an outbreak of severe dermatitis among industrial workers exposed to formaldehyde resins. Of 2,370 workers from four different plants, 355 developed dermatitis. Many of the cases required hospitalization.

In a more recent study, Fowler et al. (1992) did a retrospective evaluation of patients referred for patch testing for eczematous dermatitis thought to be allergic in nature. The patients were seen at two institutions between January 1988 and April 1990. Each patient was patch tested with commercially prepared textile allergens, the standard screening tray of the NACDG and a series of other allergens selected individually by the investigators. Of the 1,022 patients evaluated, 17 were allergic to formaldehyde resins. Five of the cases were occupationally related, and the others were related to exposure to garments treated with formaldehyde resins.

Inhalation Effects

A number of studies have been published regarding the health hazards associated with the inhalation of foam particles or free formaldehyde released from Urea Formaldehyde foam insulation both during production and after installation (Frigas et al., 1981; Lees et al., 1985; Pross et al., 1987; Elinson, 1984; Broder et al., 1988). Case reports of respiratory tract irritation have also been documented in the wood industry, where Polyoxymethylene Urea is used as a bonding agent in particle boards (Cockcroft et al., 1982; Vale and Rycroft, 1988).

Carcinogenicity

Blair et al. (1990) studied a historical cohort of 26,561 workers employed in formaldehyde industries to evaluate the cancer risks associated with exposure to formaldehyde. Formaldehyde alone could not be directly linked with elevated risks for lung cancer. The standardized mortality ratios (SMRs) for workers exposed to urea and formaldehyde ranged from 0.8 to 2.1. A control group of workers not exposed to formaldehyde had an SMR of 0.9. The SMR for workers exposed to formaldehyde alone was 1.0.

SUMMARY

Polyoxymethylene Urea is a synthetic polymer used as a bulking agent in cosmetic formulations. It is also used to make the outer shell of microcapsules. In 1993 it was reported to the FDA that Polyoxymethylene Urea was used in 28 cosmetic products, including eye shadows, perfumes, blushers, face powders, lipsticks, rouges, basecoats and undercoats, and other manicuring preparations. Polyoxymethylene Urea has been used at concentrations up to 5%.

Polyoxymethylene Urea is used in its solid form to make the outer shell of microcapsules. Impurities commonly found in Polyoxymethylene Urea are free formaldehyde, urea, monomethylolurea, methylolurea, dimethylolurea, methylenediurea, and dimethylolmethylenediurea. The amount of free formaldehyde found in Polyoxymethylene Urea microcapsules typically ranges from 17 to 30 ppm.

In acute toxicity studies, Polyoxymethylene Urea had a low order of toxicity. The oral LD_{50} for liquid Polyoxymethylene Urea in a study with rats was 10 g/kg, and the dermal LD_{50} was >2.1 g/kg. In microcapsule form, Polyoxymethylene Urea had an oral LD_{50} of 20 g/kg for rats. In dermal studies with rabbits, the LD_{50} was 5,000 mg/kg Polyoxymethylene Urea. Inhalation LC_{50} values for Polyoxymethylene Urea in studies with rats were >167 mg/m^{3}air, >2 mg/kg, and 5.0 ml/L.

An aerosol dust consisting of Polyoxymethylene Urea with cellulose decreased absolute kidney and kidney/brain weight values, increased the lung/body weight value, and caused interstitial pneumonia and, to a lesser extent, minimal, multifocal interstitial fibrosis.

Polyoxymethylene Urea was a minimal to mild skin irritant and caused mild, transient ocular irritation in studies with rabbits.

Polyoxymethylene Urea was negative in Ames tests and appeared to induce macromolecular complexes only in the presence of metabolic activation.

In a human repeated insult patch test using 50 subjects, Polyoxymethylene Urea was neither an irritant nor a sensitizer. Polyoxymethylene Urea was also classified as a nonsensitizer in a human patch test with 207 subjects. Case reports of contact dermatitis from textiles treated with formaldehyde resins have been reported in the literature. Most cases were caused by formaldehyde exposure, but some cases of contact dermatitis can be caused by the resin.

DISCUSSION

Based upon the available data, the CIR Expert Panel concluded that Polyoxymethylene Urea is safe as used. The use data that are available indicate that a 5% concentration is the greatest used. No significant adverse effects are expected in individuals exposed at this concentration.

The Panel was concerned about the release of formaldehyde from Polyoxymethylene Urea. In their review of formaldehyde in 1984, the Panel determined that formaldehyde is an irritant at low concentrations, especially to the eyes and respiratory tract. Under experimental conditions it was teratogenic and mutagenic and induced neoplasms. The Panel concluded in 1984 that the formulation and manufacture of cosmetic products should be such as to ensure use at the minimal

effective concentration of formaldehyde, not to exceed 0.2% measured as free formaldehyde. That limitation was considered appropriate for Polyoxymethylene Urea as well.

It could not be concluded in 1984 that formaldehyde is safe in cosmetic products intended to be aerosolized. Since the potential exists for formaldehyde to be released from Polyoxymethylene Urea, the Panel considers it inappropriate to use Polyoxymethylene Urea in aerosolized products.

CONCLUSIONS

On the basis of the animal, clinical, and use data presented in this report, the CIR Expert Panel concludes that Polyoxymethylene Urea is safe for use as a cosmetic ingredient. Cosmetics containing Polyoxymethylene Urea should be formulated to ensure that concentrations of free formaldehyde not exceed 0.2%. It cannot be concluded that Polyoxymethylene Urea is safe for use in cosmetic products intended to be aerosolized.

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